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In This Issue

Cinacalcet (Sensipar™): A Brief Review

Cinacalcet HCl is a novel therapeutic agent indicated for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis and the treatment of hypercalcemia in patients with parathyroid carcinoma.[1] It is also undergoing evaluation for use in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease not on dialysis, and primary hyperparathyroidism. Cinacalcet currently is not on the Clinical Center Formulary, but it is under consideration for Phase II trials at the NIH.

Clinical Pharmacology

Secondary hyperparathyroidism commonly occurs in patients with chronic kidney disease and is characterized by elevated levels of serum parathyroid hormone (PTH) and abnormalities in bone and mineral metabolism. The changes in bone and mineral metabolism are a result of abnormalities in the regulation of the intracellular and extracellular levels of PTH, calcium, phosphorus, and vitamin D. Treatment is targeted at controlling the abnormal PTH, calcium, and phosphorus levels and preventing further complications (eg, symptomatic bone disease, extraskeletal calcifications, and death).[2]

Traditional forms of therapy for secondary hyperparathyroidism have included calcium supplementation, dietary phosphorus restriction, phosphate-binding agents, vitamin D or its analogs, and surgery.[2] These forms of therapy are mainly focused at altering the PTH, calcium, and phosphorus concentrations. None of these forms of therapy have worked directly on the parathyroid or the calcium-sensing receptors within the parathyroid gland.

The secretion of parathyroid hormone, whose primary role is to maintain calcium levels by the parathyroid, is regulated by changes in extracellular calcium concentrations. When the concentration of extracellular calcium is increased, the amount of parathyroid hormone secreted by the parathyroid is reduced. When the concentration of extracellular calcium is decreased, the amount of parathyroid hormone secreted is increased. This autoregulation is controlled by calcium-sensing receptors within the parathyroid gland.[2,3]

Elevation of parathyroid hormone and hyperphosphatemia, such as that observed in patients with chronic kidney disease, results in alterations in bone production, decreased renal tubular resorption of phosphorus, increased renal tubular reabsorption of calcium, and alterations in the gastrointestinal absorption of calcium and phosphorus. These changes are designed to increase the concentration of the extracellular calcium and decrease the concentration of the phosphorus.[2]

Cinacalcet HCl is an oral calcimimetic agent. Calcimimetic compounds bind to and modulate the calcium-sensing receptors on the parathyroid gland. Their net effect is to increase the sensitivity of the receptors to calcium levels in the blood resulting in a reduction in PTH secretion from the parathyroid gland.[2,3]

Cinacalcet HCl activity is dependent both on the presence of calcium and the dose of cinacalcet HCl. In animal studies, cinacalcet HCl produced a dose-dependent reduction in ionized calcium levels. In humans, it produces dose-dependent reductions in serum parathyroid hormone and ionized calcium levels, and increases serum calcitonin levels. The mobilization of intracellular calcium is dependent on the presence of extracellular calcium.[3]

Cinacalcet HCl is about 30-fold more potent at lowering serum parathyroid hormone levels than it is at increasing serum calcitonin levels. The R-cinacalcet enantiomer is at least 75-fold more active than the S-enantiomer.[3]

Pharmacokinetics

Maximum cinacalcet plasma concentrations are reached within approximately 2 to 6 hours following oral administration.[1] The peak concentration and area under the curve (AUC) were increased 82% and 68%, respectively, when cinacalcet HCl was administered with a high-fat meal compared with fasting.[1] The peak concentration and AUC were increased 65% and 50%, respectively, when cinacalcet HCl was administered with a low-fat meal compared to fasting.[1]

Cinacalcet concentrations decline in a biphasic fashion with a terminal half-life of 30 to 40 hours. Steady-state levels are reached within 7 days. The mean accumulation ratio is approximately 2 with once-daily oral administration; median accumulation ratio is approximately 2 to 5 with twice-daily oral administration. The AUC and peak concentration increase proportionately over the dose range of 30 to 180 mg once daily. The volume of distribution is about 1000 L, representing extensive distribution. Cinacalcet is approximately 93% to 97% bound to plasma proteins.[1]

Cinacalcet undergoes metabolism by CYP3A4, CYP2D6, and CYP1A2. Plasma concentrations of the major metabolites greatly exceed cinacalcet concentrations; however, the major metabolites are inactive or have very little activity compared with cinacalcet. The metabolites are primarily excreted renally. Following administration of a radiolabeled dose, 80% of the dose was recovered in the urine and 15% in the feces.[1]

The pharmacokinetics and pharmacodynamics of cinacalcet HCl 25 mg to 300 mg doses have been assessed in patients with kidney disease requiring hemodialysis in a randomized, double-blind, placebo-controlled 7-day study. Steady state was achieved by day-4 with once-daily administration. Exposure and peak concentrations increased dose proportionally at doses up to 200 mg once daily. Increased exposure was not observed at higher doses. Parathyroid hormone levels were reduced to the greatest extent at 2 to 3 hours after oral cinacalcet HCl administration, corresponding to peak cinacalcet levels.[4]

Pharmacokinetic and pharmacodynamic data have also been compiled from 218 patients enrolled in six cinacalcet HCl clinical studies. Pharmacokinetics were described by a two-compartment model with delayed first-order absorption. Mean oral clearance (CL/F) was 234 $\pm$ 19 L/hr. Age, body weight, and body mass index did not influence cinacalcet pharmacokinetics, nor did concomitant vitamin D therapy. Gender and smoking slightly affect mean oral clearance, but because the dose is titrated individually, demographic-based dosage adjustments are not necessary.[5]

The nadir for the change in the PTH level occurs within 2 to 6 hours after oral administration. Once the steady state is achieved, the serum calcium concentration remains constant over the dosing interval in chronic kidney disease patients.[1]

Cinacalcet HCl pharmacokinetics have not been assessed in pediatric patients.[1] Cinacalcet pharmacokinetics did not differ between geriatric patients and patients who are less than 65 years of age, patients with mild, moderate, or severe renal insufficiency, or those on hemodialysis or peritoneal dialysis, and healthy volunteers.[1] Cinacalcet pharmacokinetics are comparable in patients receiving hemodialysis and chronic ambulatory peritoneal dialysis, and did not differ between hemodialysis and non-hemodialysis days.[6]

The cinacalcet HCl AUC is increased in patients with moderate-to-severe hepatic impairment compared to subjects with normal hepatic function. The AUC was 2.4 times higher in patients with moderate impairment and 4.2 times higher in patients with severe impairment. The mean cinacalcet half-life was prolonged 33% and 70% in moderate and severe impairment, respectively.

Comparative Efficacy

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative Bone Metabolism and Disease Guidelines define successful treatment of hyperparathyroidism as achievement of the following parameters:[2]

Parameter	Target Concentration
Serum iPTH	150–300 pg/mL
Serum calcium	8.4–9.6 mg/dL
Serum phosphorus	3.5–5.5 mg/dL
Calcium-phosphorus product (Ca X P)	<55 mg^2/dL^2

iPTH = intact parathyroid hormone

Secondary Hyperparathyroidism

Cinacalcet HCl was evaluated in a randomized, double-blind, placebo-controlled 26-week study enrolling 331 hemodialysis patients with secondary hyperparathyroidism (intact parathyroid hormone level of 300 pg/mL or greater). Patients received placebo or cinacalcet HCl at doses titrated from 30 to 180 mg once daily to achieve a target intact parathyroid hormone level of 250 pg/mL or less; vitamin D and phosphate binder therapy were continued as appropriate. Intact parathyroid hormone levels were reduced to 250 pg/mL or less in 46% of cinacalcet-treated patients compared with 7% of placebo-treated patients ($P<0.001$); number needed to treat 2.6. A 30% or greater reduction in intact parathyroid hormone level was achieved in 68% of patients assigned cinacalcet HCl therapy compared with 12% of placebo recipients ($P<0.001$); number needed to treat 1.8. Mean serum calcium-phosphorus product was reduced 17% in the cinacalcet group and 1% in the placebo group ($P<0.001$). Mean serum calcium was reduced 8% and phosphorus was reduced 10% in the cinacalcet group, while calcium and phosphorus remained at baseline in the placebo group ($P<0.001$).[7]

Cinacalcet HCl was also assessed in a similar 26-week placebo-controlled study enrolling 395 hemodialysis or peritoneal dialysis patients with secondary hyperparathyroidism (intact parathyroid hormone level of 300 pg/mL or greater) despite the use of standard therapy. Patients were randomized in a 3:1 ratio to either cinacalcet HCl or placebo, with doses titrated from 30 to 180 mg to achieve an intact parathyroid hormone level of 250 pg/mL or less. At baseline, mean intact parathyroid hormone was 832 pg/mL in the placebo group and 847 pg/mL in the cinacalcet group. More

cinacalcet-treated patients achieved at least a 30% reduction in parathyroid hormone levels. Results are summarized in Table 1. An intact parathyroid hormone level of 250 pg/mL or less was achieved in 36% of cinacalcet-treated patients compared with 6% of placebo-treated patients; number needed to treat is 3.3. Serum calcium, phosphorus, and calcium-phosphorus product were also reduced to a greater extent in the cinacalcet group (P<0.001).[8]

Table 1 Patients with Secondary Hyperparathyroidism Achieving at Least a 30% Reduction in Parathyroid Hormone Level in a Comparison of Cinacalcet HCl and Placebo[8]

	≤ 30% Reduction in Baseline iPTH Level	
	Placebo	Cinacalcet HCl
Hemodialysis Patients		
Baseline iPTH 300 to 500 pg/mL	24%	66%
Baseline iPTH 501 to 800 pg/mL	7%	63%
Baseline iPTH > 800 pg/mL	6%	51%
Peritoneal Dialysis Patients		
Baseline iPTH > 300 pg/mL	0%	62%

Another similar randomized, double-blind, placebo-controlled, 26-week study assessing cinacalcet HCl enrolled 410 hemodialysis patients with uncontrolled secondary hyperparathyroidism despite the use of standard therapy. Cinacalcet HCl (205 patients) or placebo (205 patients) was titrated over the range of 30 to 180 mg once daily to achieve a target intact parathyroid hormone level of 250 pg/mL or less. Parathyroid hormone level (bioactive PTH, bioPTH) was reduced by a mean of 38% in the cinacalcet group and increased by a mean of 10% in the placebo group. A 30% or greater reduction in mean parathyroid hormone was achieved in 61% of cinacalcet-treated patients compared with 11% of placebo-treated patients (P<0.001); number needed to treat is 2. BioPTH was reduced to 250 pg/mL or less in 41% of cinacalcet-treated patients compared with 4% of placebo-treated patients (P<0.001); number needed to treat is 2.7. Calcium, phosphorus, and the calcium-phosphorus product were also reduced to a greater extent in the cinacalcet group (P<0.001).[9,10]

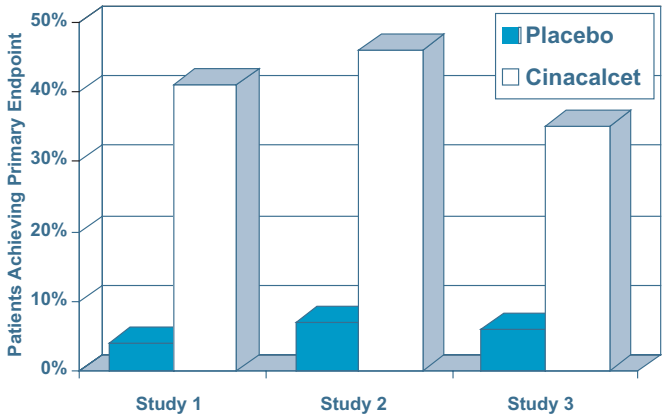
These three studies are also summarized in the cinacalcet HCl prescribing information. Overall, 665 patients were randomized to receive cinacalcet HCl and 471 were randomized to placebo. Mean patient age was 54 years, 62% were male and 52% were Caucasian, and the average duration of dialysis prior to study enrollment was 67 months. Average baseline iPTH was 712 pg/mL, with a baseline iPTH greater than 800 pg/mL present in 26% of patients. At study entry, 66% of patients were receiving vitamin D sterols and 93% were receiving phosphate binders. Cinacalcet HCl was initiated at a dose of 30 mg once daily and titrated every 3 to 4 weeks to a maximum dose of 180 mg once daily or iPTH of 250 pg/mL or less (this target level is lower than the 150 to 300 pg/mL recommended in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative [NKF-K/DOQI] Bone Metabolism and Disease Guidelines[11]). The primary endpoint was generally the proportion of patients who achieved a mean iPTH of 250 pg/mL or less during the efficacy phase of the study. The study was completed by 70% of the cinacalcet group and 80% of the placebo group. At the completion of the trial the median dose of cinacalcet HCl was 90 mg; patients with milder disease typically required lower doses. Overall, 40% of cinacalcet HCl-treated patients and 5% of placebo-treated patients achieved an iPTH of 250 pg/mL or less (P<0.001); absolute difference was 35% and the number needed to treat is 2.86. The reduction in iPTH and Ca x P were maintained for up to 12 months of treatment. Further results are summarized in Table 2.[1]

Table 2 Results from Three 6-Month Studies Assessing Cinacalcet HCl in Secondary Hyperparathyroidism[1]

	Study 1		Study 2		Study 3	
	Cinacalcet (n=166)	Placebo (n=165)	Cinacalcet (n=294)	Placebo (n=101)	Cinacalcet (n=205)	Placebo (n=205)
iPTH						
Median baseline (pg/mL)	547	556	703	670	537	535
Mean baseline (pg/mL)(SD)	652 (372)	630 (317)	848 (685)	832 (486)	636 (341)	651 (398)
Evaluation phase (pg/mL)	238	592	339	737	275	563
Median change	−54.1%	8.4%	−48.2%	2.3%	−48.3%	3.8%
Patients achieving primary endpoint (iPTH ≤ 250 pg/mL)	46%*	7%	35%*	6%	41%*	4%
Patients achieving ≥ 30% reduction in iPTH	68%	12%	59%	10%	61%	11%
Patients achieving iPTH ≤ 250 pg/mL and Ca x P < 55 mg^2/dL^2	35%	5%	28%	5%	32%	1%
Ca x P						
Baseline (mg^2/dL^2)	61	61	59	61	61	62
Evaluation phase (mg^2/dL^2)	47	59	48	57	52	59
Median change	−19.7%	−3.1%	−15.7%	−4.8%	−14.9%	−2%
Calcium						
Baseline (mg/dL)	10	9.9	9.8	9.9	9.8	9.8
Evaluation phase (mg/dL)	9.1	9.9	9.1	10	9.1	9.9
Median change	−7.4%	0.1%	−6%	0.3%	−5.5%	0.5%
Phosphorus						
Baseline (mg/dL)	6	6.1	6	6.1	6.1	6.3
Evaluation phase (mg/dL)	5.1	5.9	5.3	5.6	5.6	6
Median change	−12.4%	−2.4%	−8.6%	−5.6%	−9%	−1%

** P < 0.001 compared to placebo; P-values only presented for primary endpoint*

Figure 1 Patients Achieving Primary Endpoint (iPTH ≤ 250 pg/mL) from Three 6-Month Studies Assessing Cinacalcet HCl in Secondary Hyperparathyroidism[1]



The combined results of these three randomized, double-blind, placebo-controlled 26-week studies enrolling 1,136 dialysis patients with secondary hyperparathyroidism were also assessed with respect to achievement of proposed NKF-K/DOQI Bone Metabolism and Disease Guidelines with cinacalcet HCl therapy. Table 3 shows the combined study results for the individual bone metabolism targets.[11] The results from these three studies were also assessed for individual patient subgroups based on gender, race, age, geographic location, duration of dialysis, use of vitamin D sterols and phosphate binders at baseline, and baseline parathyroid hormone, calcium, phosphorus, and calcium-phosphorus product. In each subgroup, reductions in the parathyroid hormone level and calcium-phosphorus product were greater in the cinacalcet-treated patients than the placebo-treated patients (P<0.001). The percent change in parathyroid hormone level is summarized in Table 4.[12,13,14]

Table 4 Response to Cinacalcet HCl in Subgroup Analysis[12,13,14]

	Placebo	Cinacalcet
Mean percent change in parathyroid hormone		
Gender		
Male (n=609, 62%)	6%	-47%
Female (n=348, 38%)	12%	-46%
Race		
White (n=506, 52%)	7%	-51%
Black (n=329, 35%)	13%	-41%
Other (n=122, 13%)	2%	-47%
Age		
≥ 18, < 65 years (n=722, 74%)	11%	-49%
≥ 65 years (n=235, 26%)	2%	-49%
Geographic area		
United States (n=540, 58%)	11%	-42%
European Union (n=249, 25%)	9%	-53%
Canada (n=115, 12%)	2%	-57%
Australia (n=53, 5%)	0%	-45%
Duration of dialysis (years)		
< 1 (n=104, 11%)	-2%	-48%
1 to 5 (n=455, 48%)	8%	-46%
> 5 (n=353, 37%)	11%	-46%
Baseline parathyroid hormone (pg/mL)		
300 to 500 (n=360, 39%)	10%	-47%
501 to 800 (n=338, 35%)	8%	-53%
> 800 (n=256, 26%)	5%	-39%
Baseline Ca x P (mg²/dL²)		
< 70 (n=692, 73%)	5%	-48%
> 70 (n=265, 27%)	16%	-44%
Percentage of patients with ≥ 30% reduction in parathyroid hormone		
Vitamin D use at baseline		
Yes (n=634, 66%)	15%	78%
No (n=323, 34%)	9%	72%
Phosphate binder use at baseline		
Calcium-containing (n=375, 39%)	15%	79%
Sevelamer (n=260, 27%)	9%	73%

Table 3 Achievement of NKF-K/DOQI Bone Metabolism and Disease Targets[11]

	Placebo + Standard Therapy (n=410)		Cinacalcet HCl + Standard Therapy (n=548)		
	Baseline	Post-treatment	Baseline	Post-treatment	Number Needed to Treat
iPTH ≤ 300 pg/mL	0%	10%	0%	57%	2.1
Ca x P ≤ 55 mg²/dL²	33%	36%	37%	65%	3.5
Phosphorus ≤ 5.5 mg/dL	34%	36%	37%	54%	5.6
Calcium ≤ 9.5 mg/dL	32%	25%	32%	69%	
iPTH ≤ 300 pg/mL and Ca x P ≤ 55 mg²/dL²	0%	6%	0%	41%	2.9

iPTH = intact parathyroid hormone

Cinacalcet HCl was assessed in conjunction with standard therapy in a Phase II randomized, double-blind, placebo-controlled dose-titration study enrolling 71 hemodialysis patients with uncontrolled secondary hyperparathyroidism despite standard therapy with calcium, phosphate binders, and active vitamin D sterols. Eligible patients had a serum calcium of 8.8 mg/dL or greater, but less than 11 mg/dL, serum phosphorus of 2.5 mg/dL or greater, and a calcium-phosphorus product less than 70 $(mg/dL)^2$. Mean baseline parathyroid hormone was 626 pg/mL in the cinacalcet group and 583 pg/mL in the placebo group. Vitamin D sterols were in use in 61% of patients in the cinacalcet group and 69% in the placebo group at the start of the study. Phosphate binders were in use at the start of the study in 100% of patients in the cinacalcet group and 94% in the placebo group. Patients were randomized to therapy with once-daily cinacalcet HCl (36 patients) or placebo (35 patients). Cinacalcet HCl doses were escalated over the first 12 weeks of the study from 25 mg, to 50 mg, 75 mg, and 100 mg, with the dose increased until patients achieved both a reduction in parathyroid hormone of 30% or greater from baseline and an absolute parathyroid hormone level of 250 pg/mL or less. The final dose from the titration phase was continued for an additional 6 weeks, with some patients continuing therapy for up to 1 year. In the 34 patients completing the cinacalcet HCl dose titration, 50% reached the 100 mg dose, while 41% of patients reached 75 mg or 50 mg doses, and 9% did not escalate beyond the 25 mg dose. The mean final dose was 74 mg. Mean parathyroid hormone concentration decreased by 33% in the cinacalcet group at 24 hours after dosing compared with an increase of 3% in the placebo group (P=0.001). Mean parathyroid hormone level was reduced to 250 pg/mL or lower in 44% of cinacalcet-treated patients compared with 20% of placebo-treated patients (P=0.029); number needed to treat is 4.2. A reduction in parathyroid hormone level of 30% or greater occurred in 53% of cinacalcet-treated patients and 23% of placebo-treated patients (P=0.009); number needed to treat is 3.3. Calcium-phosphorus product levels decreased by 7.9% in the cinacalcet group, but increased by 11.3% in the placebo group (P=0.013). At 1 year, lumbar spine bone mineral density was reduced 1.1% in the placebo group and unchanged in the cinacalcet group. Femoral neck bone mineral density was increased 0.2% in the placebo group and 2% in the cinacalcet group. Total body bone mineral density was reduced 1.6% in the placebo group and increased 0.5% in the cinacalcet group.[15,16]

Another Phase II study enrolled 78 hemodialysis patients with secondary hyperparathyroidism into an 18-week, double-blind, randomized, placebo-controlled dose-titration study. These patients had to have an iPTH value greater or equal to 300 pg/mL despite treatment with a phosphate binder and/or vitamin D sterol. The remainder of the inclusion criteria was very similar to the previous Phase II study. All patients continued their previous therapy, but the dose could be adjusted following predetermined guidelines. Patients were randomized 1:1 to treatment with cinacalcet HCl or placebo. The start dose of cinacalcet HCl was 20 mg once daily. This dose was adjusted every 3 weeks until the iPTH value was reduced by 30% or more from baseline and to less than or equal to 250 pg/mL, unless the patient's serum calcium level dropped below 7.8 mg/dL or they developed symptoms of hypocalcemia. The dose of cinacalcet HCl could be adjusted up to 30, 40, or 50 mg per day or down to 10 mg per day depending on the iPTH response. If the iPTH value dropped below 100 pg/mL on two successive weekly visits, the dose of the study medication was decreased. The primary endpoint was the proportion of patients that achieved a reduction in the iPTH by 30% or greater during the maintenance phase of the study. Secondary endpoints included percent change from baseline in the iPTH, serum calcium, phosphorus, and calcium x phosphorus levels during the maintenance phase. The average change in the iPTH was a 26% decrease in the cinacalcet group and 22% increase in the placebo group (P<0.001). The primary endpoint was achieved by 38% in the cinacalcet group and 8% in the placebo group (P<0.001). The cinacalcet group also had better changes in a secondary endpoints.[17]

The effects of cinacalcet HCl were also assessed in a two-part, randomized, double-blind, placebo-controlled study enrolling 51 hemodialysis patients with secondary hyperparathyroidism. During the first phase of the study, patients received a single dose of cinacalcet HCl 5 mg (8 patients), 10 mg (8 patients), 25 mg (6 patients), 50 mg (6 patients), 75 mg (6 patients), or 100 mg (6 patients), or placebo (12 patients). During the multiple-dose phase, patients were randomized to received cinacalcet HCl 10 mg (8 patients), 25 mg (6 patients), 50 mg (9 patients), or placebo (7 patients) once daily for 8 days. During the single-dose phase, plasma parathyroid hormone levels declined within a few hours in patients receiving cinacalcet HCl doses of 25, 50, 75, or 100 mg, but were unchanged in patients receiving cinacalcet HCl 5 mg or 10 mg or placebo. Maximal reductions observed within 2 to 4 hours after administration were 57% in the 25 mg group, 59% in the 50 mg group, 59% in the 75 mg group, and 72% in the 100 mg group. Serum total calcium declined slightly in patients in the highest two dosage groups, reaching lowest levels 8 to 12 hours after dosing and remaining below pretreatment levels for 24 hours. With daily administration for 8 days, reductions in parathyroid hormone were observed in patients treated with the 25 mg and 50 mg doses. Parathyroid hormone was reduced 39.6% in the 25 mg group and 44.5% in the 50 mg group at 2 hours after administration on day-1 and by 42% in the 25 mg group and 32% in the 50 mg group at 4 hours after administration on day-8. At 24 hours after administration on the eighth day, plasma parathyroid hormone levels were reduced 28% in the 25 mg group and 27% in the 50 mg group. Calcium, phosphorus, and calcium-phosphorus ion product values were also reduced slightly in the cinacalcet-treatment groups.[18]

Another double-blind study assessed cinacalcet HCl compared with placebo in the treatment of secondary hyperparathyroidism in 54 patients with chronic renal disease not yet receiving dialysis (creatinine clearance 15 to 50 mL/min). At baseline, mean intact parathyroid hormone levels were 236 pg/mL in the placebo group and 243 pg/mL in the cinacalcet group. Only 28% of patients were receiving vitamin D sterols and 22% were receiving phosphate binders. Patients were randomized to therapy with cinacalcet HCl or placebo at doses titrated from 30 mg to 180 mg once daily to obtain a 30% or greater reduction in intact parathyroid hormone level. At weeks –13 to –18, intact parathyroid hormone level was increased by a mean of 5% in the placebo group and reduced by a mean of 37% in the cinacalcet group ($P<0.001$). Intact parathyroid hormone was reduced at least 30% in 19% of patients in the placebo group and 56% of patients in the cinacalcet group ($P=0.01$).[19]

Patients from three 1-year randomized, placebo-controlled studies of cinacalcet HCl were eligible for enrollment in a long-term extension study during which all patients received cinacalcet HCl. Patients previously treated with placebo were titrated on cinacalcet HCl at doses from 30 mg to 180 mg once daily. Vitamin D and phosphate binder use was allowed to be adjusted during the study. Two years of therapy was completed by 59 patients. Mean serum parathyroid hormone was 590 pg/mL at baseline, 437 pg/mL at 52 weeks, and 451 pg/mL at 100 weeks. A parathyroid hormone level of 300 pg/mL or less was achieved in 52% of patients at 52 weeks and 59% of patients at 100 weeks. A 30% or greater reduction in parathyroid hormone was achieved in 57% of patients at 52 weeks and 66% at 100 weeks of the open-labeled extension study. Mean calcium-phosphorus product was unchanged ($56.4\ mg^2/dL^2$ at baseline, $54\ mg^2/dL^2$ at 52 weeks, and $55.1\ mg^2/dL^2$ at 100 weeks).[20] These data indicate that cinacalcet is effective at lowering the iPTH and maintaining the calcium-phosphate product for up to 3 years.

Primary Hyperparathyroidism

Cinacalcet HCl was evaluated in a randomized, double-blind, placebo-controlled study enrolling 78 patients with primary hyperparathyroidism and calcium levels between 10.3 mg/dL and 12.5 mg/dL. Patients were randomized to therapy with either placebo or cinacalcet HCl 30 mg twice daily. Doses were titrated as needed over 12 weeks to a maximum dose of 50 mg twice daily, then continued at a fixed dose for an additional 12 weeks. A reduction in serum calcium of at least 0.5 mg/dL and a reduction to a predose serum calcium of 10.3 mg/dL or less during the maintenance phase were achieved in 88% of cinacalcet-treated patients compared with 5% of placebo-treated patients. During the maintenance phase, parathyroid hormone levels were reduced 7.6% at 12 hours post-dose in the cinacalcet group as compared with an increase of 7.7% at 12 hours post-dose in the placebo group.[21] After the completion of this phase of the study, the patients continued in this randomized, double-blind, placebo-controlled study for 1 year. Forty-five patients completed 1 year of double-blind therapy and entered an open-label extension phase in which all patients received cinacalcet HCl. Mean serum calcium levels rapidly dropped within the normal range upon initiation of cinacalcet HCl therapy during the double-blind phase of the study or upon switching from placebo to cinacalcet HCl in the open-label extension. Thirty-nine patients remained in the study for 3 years and 87% of those patients had serum calcium levels within the normal range. Mean pre-dose intact parathyroid hormone level was reduced 7% from baseline. Bone mineral density was unchanged from baseline. Approximately 60% of patients remained on a cinacalcet HCl dose of 30 mg twice daily.[22]

Cinacalcet HCl was assessed in a randomized, double-blind, placebo-controlled, dose-finding study enrolling 22 patients with primary hyperparathyroidism (parathyroid hormone concentration of 45 pg/mL or greater on at least two occasions during the preceding 12 months and two serum calcium concentrations between 10.3 and 12.5 mg/dL). Patients were treated with cinacalcet HCl 30 mg (5 patients), 40 mg (6 patients), or 50 mg (5 patients) or placebo (6 patients) twice daily for 15 days, then observed for an additional 7 days. Baseline mean serum calcium was 10.6 mg/dL in the cinacalcet group and 10.4 mg/dL in the placebo group. Mean parathyroid hormone at baseline was 102 pg/mL (normal range 10-65 pg/mL) in the cinacalcet group and 100 pg/mL in the placebo group. In the cinacalcet-treated patients, mean serum calcium was reduced into the normal range 2 hours after the second dose on day-1 and remained within the normal range through the last dose on day-15. At day-8 serum calcium was reduced 10% from baseline (10.6 to 9.5 mg/dl) in the combined cinacalcet group but was increased 3% (10.4 to 10.7 mg/dL) in the placebo group. Prior to dosing on day-15, serum calcium was reduced 11% in the 30 mg group, 18.7% in the 40 mg group, and 18.5% in the 50 mg group, compared with a 0.3% increase in the placebo group ($P<0.05$ for the 40 mg dose). Combined results for the cinacalcet group revealed a mean 16% reduction in mean serum calcium ($P=0.004$ vs placebo). A maximum reduction in parathyroid hormone of over 50% occurred 2 to 4 hours after dosing in all cinacalcet groups. The mean parathyroid hormone value 4 hours after the first dose was reduced 46.9% from baseline in the combined cinacalcet group, compared with a 2.6% reduction in the placebo group. Parathyroid hormone levels were reduced below baseline throughout the 12-hour dosing interval in each cinacalcet group; however, immediately prior to the next dose parathyroid levels did not differ significantly from those in the placebo group. On day-15, the mean reduction in parathyroid hormone at 4 hours after dosing was 50.4% in the cinacalcet HCl 30 mg group, 48.8% in the cinacalcet HCl 40 mg group, 50.6% in the cinacalcet HCl 50 mg group, compared with an increase of 0.3% in the placebo group ($P=0.033$ for 30 mg, $P=0.023$ for 40 mg, $P=0.052$ for 50 mg). Mean parathyroid hormone levels prior to the next dose on day-15 were reduced 20.3% in the combined cinacalcet

group and by 1.8% in the placebo group (P=0.07). Fasting and 24-hour urine calcium to creatinine ratios were similar in the cinacalcet and placebo groups. Cinacalcet HCl normalized serum calcium and lowered parathyroid hormone without increasing urinary calcium excretion.[23] In a previous phase of this study, once-daily cinacalcet HCl at 50 mg to 100 mg doses was assessed. Maximal reductions in parathyroid hormone of 59.4% at 2 hours after dosing and 38.5% at 4 hours after dosing were achieved. However, reductions were not maintained over the day. A high incidence of nausea and dizziness also precluded once-daily dosing.[23]

Experience with cinacalcet HCl was also described in an open-label, dose-titration study enrolling six patients with parathyroid carcinoma and two patients with recurrent primary hyperparathyroidism following parathyroidectomy. All patients had a serum calcium level greater than 12.5 mg/dL. Doses were titrated over a range from 30 mg twice daily to 90 mg four times daily to achieve a reduction in serum calcium of at least 1 mg/dL. The titration phase lasted 16 weeks or until serum calcium was 10.3 mg/dL or less. Mean serum calcium was reduced from 14.8 mg/dL at baseline to 11.2 mg/dL at the end of the titration phase. A reduction in serum calcium of at least 1 mg/dL was achieved in 6 of 8 patients (75%). Pre-dose intact parathyroid hormone levels were not reduced; however, reductions in parathyroid hormone levels were observed at 2 and 4 hours after dosing.[24,25]

The cinacalcet HCl prescribing information also contains the results of an open-label study of cinacalcet HCl in 10 patients with parathyroid carcinoma. Ten patients received cinacalcet HCl for 2 to 16 weeks in the titration phase, and three patients continued to receive cinacalcet HCl for 16 to 48 weeks during the maintenance phase. Doses ranged from 70 mg twice daily to 90 mg four times daily in the maintenance phase. Baseline mean serum calcium was 14.7 mg/dL. The range of change from baseline to last measurement was –7.5 to 2.7 mg/dL during the titration phase and –7.4 to 0.9 mg/dL during the maintenance phase. No patients maintained serum calcium within the normal range.[1]

Contraindications

Cinacalcet HCl is contraindicated in patients with a history of hypersensitivity to the agent or its excipients (pre-gelatinized starch, microcrystalline cellulose, povidone, crospovidone, colloidal silicon dioxide, and magnesium stearate).[1]

Warnings and Precautions

Serum calcium levels should be closely monitored throughout therapy and patients should be monitored for symptoms of hypocalcemia. Therapy with cinacalcet HCl should not be initiated in patients with serum calcium lower than the lower limit of the normal range (8.4 mg/dL). Serum calcium should be measured within 1 week after initiation of therapy and subsequent dosage adjustments. Once a maintenance dose has been established, serum calcium should be measured approximately once a month. If serum calcium falls below 8.4 mg/dL, but remains above 7.5 mg/dL, or if symptoms of hypocalcemia occur, calcium-containing phosphate binders and/or vitamin D sterols can be used to raise serum calcium. If serum calcium falls below 7.5 mg/dL or if symptoms of hypocalcemia persist and the dose of vitamin D cannot be increased, cinacalcet HCl therapy should be withheld until serum calcium reaches 8 mg/dL and/or symptoms have resolved. Treatment should be restarted using the next lowest cinacalcet HCl dose.[1] In the three pivotal studies of cinacalcet HCl in patients with secondary hyperparathyroidism, 66% of cinacalcet HCl-treated patients and 25% of placebo-treated patients developed at least one serum calcium level less than 8.4 mg/dL. Less than 1% of patients in each group required permanent discontinuation of therapy due to hypocalcemia.[1]

The long-term safety and efficacy of cinacalcet HCl in patients with chronic kidney disease and secondary hyperparathyroidism who are not on dialysis have not been established. Preliminary studies suggest such patients may be at an increased risk for hypocalcemia.[1]

In clinical trials, seizures occurred in 1.4% of patients treated with cinacalcet HCl (9/656) and 0.4% of patients treated with placebo (2/470). Five of the 9 patients in the cinacalcet HCl group and both patients in the placebo group had a history of seizure disorder. Seizure threshold is lowered by significant reductions in serum calcium levels. Serum calcium levels should be closely monitored in patients with a history of seizure disorder.[1]

Adynamic bone disease may occur if iPTH levels are suppressed below 100 pg/mL. If iPTH levels decline below 150 to 300 pg/mL during cinacalcet HCl therapy, the dose of cinacalcet HCl and/or vitamin D sterols should be reduced or therapy discontinued.[1]

Cinacalcet HCl exposure is increased in patients with moderate-to-severe hepatic impairment. Such patients should be closely monitored during cinacalcet HCl therapy.[1]

Cinacalcet HCl has not been studied in children.[26]

Cinacalcet HCl is in Pregnancy Category C. Teratogenicity was not observed in animal studies; decreased fetal body weights were observed in conjunction with maternal toxicity. Cinacalcet HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.[1]

In studies in rats, cinacalcet HCl was observed to be excreted in milk with a high milk-to-plasma ratio. It is not known if cinacalcet HCl is excreted in human milk. A decision should be made to discontinue nursing or discontinue cinacalcet HCl, taking into account the importance of the drug to the lactating woman.[1]

Adverse Reactions

Adverse reactions observed during cinacalcet HCl therapy have most commonly included nausea and vomiting.[1,15,20,23,25,26] Gastrointestinal side effects have been observed more frequently in patients treated with cinacalcet HCl than placebo-treated patients.[7,8,19] Nausea is particularly common at the doses required to treat

primary hypercalcemia, necessitating discontinuation of therapy in some patients.[25]

The incidence or nature of adverse events associated with cinacalcet HCl therapy during 12 months[1] and 3 years[20] of therapy have been similar to those observed in the Phase III studies.

Serum testosterone levels were observed to decline during cinacalcet HCl therapy; however, testosterone levels are often below the normal range in patients with end-stage renal disease. In patients with chronic kidney disease on dialysis, total cholesterol declined by a median of 15.8% in patients treated with cinacalcet HCl for 6 months compared with a 0.6% reduction in placebo-treated patients. Free testosterone declined by a median of 31.3% in the cinacalcet HCl-treated patients and 16.3% in the placebo-treated patients. The clinical importance of these reductions is unknown.[1]

Drug Interactions

Cinacalcet HCl is a potent inhibitor of CYP2D6, but not of CYP1A2, CYP2C9, CYP2C19, or CYP3A4.[1] In extensive CYP2D6 metabolizers, concurrent administration of cinacalcet HCl with amitriptyline increased amitriptyline and nortriptyline exposure by about 20%.[1] Dosage adjustments of concomitant medications metabolized by CYP2D6 and with a narrow therapeutic index is recommended (eg, flecainide, vinblastine, thioridazine, most tricyclic antidepressants).[1]

Cinacalcet HCl is metabolized by CYP3A4, CYP2D6, and CYP1A2.[1] Administration of ketoconazole with cinacalcet HCl resulted in a 2.3-fold increase in cinacalcet AUC and a 2.2-fold increase in cinacalcet peak concentration compared with administration of cinacalcet HCl alone.[1] When initiating or discontinuing therapy with a strong CYP3A4 inhibitor (eg, ketoconazole, erythromycin, itraconazole), cinacalcet HCl dosage adjustments may be required and serum calcium and iPTH concentrations should be closely monitored.[1]

Cinacalcet HCl absorption was not affected by concomitant administration with pantoprazole, sevelamer, or calcium carbonate.[1,27] Warfarin pharmacokinetics and pharmacodynamics were not affected by concomitant administration of cinacalcet HCl.[1]

Recommended Monitoring

In patients with chronic kidney disease on dialysis and secondary hyperparathyroidism, serum calcium and serum phosphorus should be measured within 1 week and iPTH should be measured 1 to 4 weeks after initiation or dose adjustment. Once the maintenance dose has been established, serum calcium and serum phosphorus should be measured about once a month and iPTH should be assessed every 1 to 3 months.[1]

In patients with parathyroid carcinoma, serum calcium should be measured within 1 week after initiation and each dosage adjustment. Once the maintenance dose has been established, serum calcium should be measured every 2 months.[1]

Dosing

Cinacalcet HCl should be taken with food or shortly after a meal.[1] The product labeling recommends cinacalcet HCl tablets be taken whole and not divided.[1]

In patients with chronic kidney disease on dialysis and secondary hyperparathyroidism, the recommended starting dose of cinacalcet HCl is 30 mg once daily. Serum calcium and serum phosphorus should be measured within 1 week and iPTH should be measured 1 to 4 weeks after initiation of dosage adjustment. The dose should be titrated no more frequently than every 2 or 4 weeks through sequential doses of 60, 90, 120, and 180 mg once daily to target iPTH of 150 to 300 pg/mL.[1]

In patients with parathyroid carcinoma, the recommended starting dose is 30 mg twice daily. The dosage should be titrated every 2 to 4 weeks through sequential doses of 30 mg twice daily, 60 mg twice daily, 90 mg twice daily, and 90 mg three or four times daily as necessary to normalize serum calcium.[1]

Dosage adjustments are not necessary in geriatric patients or patients with impaired renal function. Patients with moderate-to-severe hepatic impairment may require lower dosages of cinacalcet HCl; however, the dose should be determined through individual dosage titration.[1]

Product Availability and Storage

Cinacalcet HCl received FDA approval in March 2004, following submission of a New Drug Application in September 2003.[28] It is available as 30-mg, 60-mg, and 90-mg tablets.[1] Currently, this product is not on the Clinical Center Formulary.

Conclusion

Cinacalcet HCl is a promising addition to the therapy of primary and secondary hyperparathyroidism and parathyroid carcinoma. It is the first calcimimetic agent approved by the Food and Drug Administration. Unlike previous therapies, cinacalcet HCl works directly at the calcium-sensing receptor in the parathyroid gland resulting in a reduction in PTH, Ca x P, serum calcium, and serum phosphorus concentrations. All patients should have their calcium level monitored closely during therapy. Cinacalcet HCl appears effective when used alone or in conjunction with standard therapies (vitamin D sterols and/or phosphate binders) for the treatment of secondary PTH in patients with chronic kidney disease. Cinacalcet HCL is well tolerated. The most common adverse effects associated with cinacalcet HCl therapy are nausea and vomiting; these adverse effects occur more frequently in patients treated with cinacalcet HCL compared to placebo. Cinacalcet HCl may allow more patients to achieve the goals established by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative clinical guidelines for bone metabolism and disease in chronic kidney disease.

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Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary changes:

Additions

- Letrozole (Femara), an oral, non-steroidal aromatase inhibitor for treatment of advanced breast cancer
- Cyclosporine (Restasis), an ophthalmic emulsion indicated for patients with keratoconjunctivitis sicca
- Alemtuzumab (Campath), an injectable humanized monoclonal antibody for treatment of B-cell chronic lymphocytic leukemia, refractory T-cell prolymphocytic leukemia, and T-cell and B-cell Non-Hodgkin's Lymphoma

Deletions

- Epifrin ophthalmic solution

FDA Safety Alerts

- You can access the latest safety information from the Food and Drug Administration website. To access "Dear Health Professional" letters, other safety notifications, and labeling changes related to drug safety, just point your browser to *www.fda.gov* and click on "MedWatch." MedWatch is the FDA's medical products reporting program.

- You can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website. Just send a subscription message to *fdalists@archie.fda.gov.* In the message body enter: *subscribe medwatch* and your e-mail address.

Drug Information Service

- Patient-specific pharmacotherapy evaluation and management
- Comprehensive information about medications, biologics, and nutrients
- Critical evaluation of drug therapy literature
- Assistance with study design and protocol development
- Clinical trial drug safety monitoring
- Investigational drug information
- Parenteral nutrition assessment and management

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